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In re Patent No.: US 6,936,584 B1

Issue Date:	August 30, 2005	**Art Unit:**	1639
Applicants:	Nigel R.A. Beeley et al.	**Examiner:**	B. Celsa
Serial No.:	09/622,104		
Filed:	July 16, 2001		
Title:	**Novel Mixed Amylin Activity Compounds**		

REQUEST FOR CERTIFICATE OF CORRECTION

Attention Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants hereby request a Certificate of Correction under 37 C.F.R. § 1.322 regarding U.S. Patent No. 6,936,584 B1, issued August 30, 2005. The following documents are enclosed for your review and consideration:

1. Certificate of Correction - 1 page
2. Copy of USPTO Response to Rule 312 Communication - 2 pages
3. Pages from subject patent highlighting corrections to be made and corrections to be inserted – 2 pages

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CERTIFICATE OF MAILING
(37 C.F.R. §1.10)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage in an envelope addressed to :Attention Certificate of Correction, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Amanda J. Halverson
Name of Person Mailing Paper

November 21, 2005
Date of Deposit

Amanda J. Halverson
Signature of Person Mailing Paper

In support of Applicants request to correct the 35 USC § 371(c), (1), (2), (4) date, the Patent Office in their Response to Rule 312 Communication dated July 1, 2005 (copy attached), accepted Applicants request for a corrected filing receipt indicating the correct filing date under 35 USC § 371(c), (1), (2), (4) as July 16, 2001. Therefore, Jul. 17, 2001 should be removed and Jul. 16, 2001 inserted.

Additionally, in support of Applicants request to correct claim 19, the Patent Office allowed claims 1-25 in the Notice of Allowability mailed January 19, 2005. Claim 19, as originally filed, indicated dependency on claims 1 to **18** and remained as the original claim throughout the prosecution of this patent. Therefore, in claim 19 the number 8 should be removed and 18 inserted as originally filed.

Applicants believe that the errors are due to mistakes on the part of the Patent Office and therefore do not believe any fees are due with this submission. However, if any fees should become due in connection with this submission the Commissioner is hereby authorized to charge any additional fees or credit any overpayment to Applicant's Deposit Account No. 010535. A duplicate of this sheet is enclosed for this purpose.

Respectfully submitted,

AMYLIN PHARMACEUTICALS, INC.

Dated: 21 November 2005

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : US 6,936,584

APPLICATION NO.: 09/622,104

ISSUE DATE : August 30, 2005

INVENTOR(S) : Nigel R.A. Beeley, Kathryn Prickett, Kevin Beaumont

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

1. Page 1 (cover page), column 1, section labeled (86) third line, "Jul. 17, 2001" should be changed to --Jul.16, 2001--.

2. Column 46, claim 19, line 7, "8" should be changed to --18--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

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US006936584B1

(12) **United States Patent**
Beeley et al.

(10) **Patent No.: US 6,936,584 B1**
(45) **Date of Patent: Aug. 30, 2005**

(54) **MIXED AMYLIN ACTIVITY COMPOUNDS**

(75) Inventors: **Nigel R. A. Beeley**, Solana Beach, CA (US); **Kathryn Prickett**, San Diego, CA (US); **Kevin Beaumont**, San Diego, CA (US)

(73) Assignee: **Amylin Pharmaceuticals, Inc.**, San Diego, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/622,104**

(22) PCT Filed: **Feb. 5, 1999**

(86) PCT No.: **PCT/US99/02603**

§ 371 (c)(1),
(2), (4) Date: **Jul. 17, 2001** Jul. 16, 2001

(87) PCT Pub. No.: **WO99/40928**

PCT Pub. Date: **Aug. 19, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/074,746, filed on Feb. 13, 1998.

(51) **Int. Cl.**[7] **A61K 37/02**; C07K 7/10
(52) **U.S. Cl.** **514/12**; 514/866; 530/324
(58) **Field of Search** 530/324; 514/12, 514/866

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(Continued)

Primary Examiner—Bennett Celsa
(74) *Attorney, Agent, or Firm*—Arnold & Porter LLP

(57) **ABSTRACT**

Compounds which inhibit certain activities of amylin but which also act as amylin agonists with respect to other amylin activities are disclosed. Such compounds are useful in treating disturbances in fuel metabolism in mammals, including but not limited to, diabetes, mellitus, including Type I diabetes and Type II diabetes, impaired glucose tolerance, insulin resistance and Syndrome X. The present invention also relates to methods of treating Type I diabetes, beneficially regulating gastrointestinal motility, treating impaired glucose tolerance, treating postprandial hyperglycemia, treating obesity and treating Syndromne X, comprising administration of a therapeutically effective amount of certain compounds, as described herein.

25 Claims, 17 Drawing Sheets

-continued

<222> LOCATION: (7)
<223> OTHER INFORMATION: Xaa stands for NH2

<400> SEQUENCE: 31

Val Gly Ser Asn Thr Tyr Xaa
1 5

<210> SEQ ID NO 32
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<222> LOCATION: (7)
<223> OTHER INFORMATION: Xaa stands for NH2

<400> SEQUENCE: 32

Val Gly Ser Gly Thr Pro Xaa
1 5

We claim:

1. A compound of the formula:

X_1-X_2-X_3-Leu-X_4-Glu-Leu-X_5-X_6-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-X_7-Z_3 [SEQ.ID.NO.27]

wherein:

(a) X_1 is

(i) a group of two amino acid residues selected from the group consisting of Leu-Leu, Val-Leu, Ile-Leu, tert-Leu-Leu, Nle-Leu, and Ala-Thr, and N-acylated derivatives thereof; or

(ii) the group Z_1-Ser-Thr-Z_2-Val-Leu [SEQ.ID.NO. 28] wherein Z_1 is an amino acid residue selected from the group consisting of Leu, Val, Ile, tert-Leu, Nva, Abu, and Nle or an N-acylated derivative thereof or Z_1 is an alkanoyl group; and Z_2 is a amino acid residue selected from the group consisting of Ala, Ser, Cys, and Thr;

(b) X_2 is an amino acid residue selected from the group consisting of Gly, Glu, Asn or Aib;

(c) X_3 is an amino acid residue selected from the group consisting of Arg, Orn, Lys and ϵ-amidated derivatives thereof;

(d) X_4 is a group of two amino acid residues selected from the group consisting of Ser-Gln, Thr-Gln, Ala-Asn and Thr-Asn;

(e) X_5 is an amino acid residue selected from the group consisting of His, Aib, Ile, Leu and Val;

(f) X_6 is an amino acid residue selected from the group consisting of Arg, Orn and Lys and ϵ-amidated derivatives thereof;

(g) X_7 is a group having 6 amino acid residues selected from the group consisting of

(i) Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 29];

(ii) Thr-Gly-Ser-Gly-Thr-Pro [SEQ.ID.NO. 30];

(iii) Val-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 31];

(iv) Val-Gly-Ser-Gly-Thr-Pro [SEQ.ID.NO. 32]; and

(h) Z_a is OH or NH_2;

with the proviso that the compound does not have the formula of any of SEQ. ID. NOS. 14 to 26; and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein Z_3 is NH_2.

3. A compound according to claim 1 wherein X_2 is Gly.

4. A compound according to claim 3 wherein X_5 is His or Aib.

5. A compound according to claim 4 wherein X_4 is Ser-Gln.

6. A compound according to claim 5 wherein X_7 is Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 29] or Thr-Gly-Ser-Gly-Thr-Pro-NH_2 [SEQ.ID.NO. 30].

7. A compound according to claim 6 wherein X_1 is Z_1-Ser-Thr-Z_2-Val-Leu [SEQ.ID.NO.28].

8. A compound according to claim 7 wherein X_3 and X_6 are ϵ-amidated with a carboxylic acid having 1 to 8 carbon atoms.

9. A compound according to claim 1 wherein Z_1 is an alkanoyl group having 1 to about 10 carbon atoms or Leu.

10. A compound according to claim 9 wherein Z_2 is Ala or Cys.

11. A compound according to claim 10 wherein Z_1 is an alkanoyl group.

12. A compound according to claim 11 wherein X_3 and X_6 are formamidated or acetamidated.

13. A compound according to claim 12 wherein Z_2 is Ala.

14. A compound according to claim 13 wherein X_3 and X_6 are Lys(For).

15. A compound according to claim 14 wherein Z_1 is 4-methylpentanoyl.

16. A compound according to claim 1 which has an amino acid sequence selected from the group consisting of:

Leu-Ser-Thr-Cys-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 1];

4-methylpentanoyl-Ser-Thr-Ala-Val-Leu-Aib-Lys(For)-Leu-Ser-Gln-Glu-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro [SEQ.ID.NO. 2];

Ac-Leu-Ser-Thr-Ser-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 3];

Leu-Ser-Thr-Ala-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 4];

Leu-Ser-Thr-Ser-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 5];

Ac-Leu-Ser-Thr-Ala-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 6];

Ac-Leu-Ser-Thr-Cys-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 7];

Val-Leu-Aib-Lys(For)-Leu-Ser-Gln-Gl-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 8];

Ac-Val-Leu-Aib-Lys(For)-Leu-Ser-Gln-Glu-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 9];

4-methylpentanoyl-Ser-Thr-Ala-Val-Leu-Aib-Lys(For)-Leu-Ser-Gln-Glu-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 10];

4-methylpentanoyl-Ser-Thr-Cys-Val-Leu-Aib-Lys(For)-Leu-Ser-Gln-Glu-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 11];

Ala-Thr-Aib-Lys(For)-Leu-Ala-Asn-Glu-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 12];

and

Ac-Ala-Thr-Aib-Lys(For)-Leu-Ala-Asn-Glu-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 13].

17. The compound Leu-Ser-Thr-Cys-Val-Leu-Gly-Arg-Leu-Ser-Gln-Glu-Leu-His-Arg-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Asn-Thr-Tyr [SEQ.ID.NO. 1].

18. The compound 4-methylpentanoyl-Ser-Thr-Ala-Val-Leu-Aib-Lys(For)-Leu-Ser-Gln-Glu-Leu-Aib-Lys(For)-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro [SEQ.ID.NO. 2].

19. A composition comprising a compound of any of claims **1** to **8** in a pharmaceutically acceptable carrier.

20. A method of treating diabetes in a subject in need of treatment which comprises administering to said subject a therapeutically effective amount of a compound of any of claim **1**, **2**, **15**, **16**, **17** or **18**.

21. A method according to claim **20** wherein said diabetes is type I diabetes.

22. A method according to claim **20** wherein said diabetes is type II diabetes.

23. A method of beneficially regulating gastrointestinal motility in a subject comprising administering to said subject a therapeutically effective amount of a compound of any of claim **1**, **2**, **15**, **16**, **17** or **18**.

24. A method according to claim **23** wherein said beneficial regulation of gastrointestinal motility comprises delaying gastric emptying.

25. A method of treating a disorder selected from the group consisting of: impaired glucose tolerance; postprandial hyperglycemia; obesity; and Syndrome x; in a subject in need of treatment which comprises administering to said subject a therapeutically effective amount of a compound of any of claim **1**, **2**, **15**, **16**, **17** or **18**.

* * * * *

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09/622,104	07/17/2001	Nigel R.A. Beeley	030639.0057.US	8378

44638 7590 07/01/2005

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EXAMINER	
CELSA, BENNETT M	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Response to Rule 312 Communication	Application No.	Applicant(s)	
	09/622,104	BEELEY ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☒ The amendment filed on *18 April 2005* under 37 CFR 1.312 has been considered, and has been:

   a) ☒ entered.

   b) ☐ entered as directed to matters of form not affecting the scope of the invention.

   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
   Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

   d) ☐ disapproved. See explanation below.

   e) ☐ entered in part. See explanation below.

The Bibliographic Sheet information has been revised to indicate 7/16/01 filing date of present application and Office of Initial Patent Examination (OIPE) has been notified as to corrected filing receipt.

6/23/05

Bennett Celsa
Primary Examiner
Art Unit: 1639